Subst. D3

C7 cont'd

a third component comprising a pharmaceutically tolerated excipient;

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.3% to about 50% of the first component, and wherein the disease is atopic dermatitis, asthma, urticaria, rhinitis, uveitis, type II diabetes, cystic fibrosis, colitis, or hepatic fibrosis.

REMARKS

Claims 12-17, 20-26, and 29 are currently pending in this application. Claims 18, 19, 27, and 28 have been cancelled without prejudice or disclaimer of the subject matter contained therein. Applicants reserve the right to file a continuation application. Claims 12, 20, and 26 have been amended to correct the typographical error introduced in formula I by a printing error. Support for this amendment can be found in the specification at page 2, and original claim 1. Claims 13-17 and 22-25 have been amended to correct the dependency of these claims. No new matter has been introduced by these amendments.

I. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 13-19, 22-25, 28, and 29 have been rejected as being indefinite for failing to particularly and distinctly claim that which Applicants regard as their invention.

Claims 13-19 and 29 have been rejected as improperly referring to the canceled claim 1. Applicants have amended claims 13-17 and claim 29 have been amended to depend from claim 12. Claims 17 and 18 have been canceled.

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Claims 22-25 and 28 have been rejected as improperly referring to a composition claim. Claims 22-25 have been amended to correct their dependency. Claim 28 has been canceled.

Claims 18 and 19 have been canceled, thereby rendering the rejection of these claims moot.

In view of these amendments and cancellations, Applicants request that the rejections under § 112, second paragraph, be withdrawn.

II. Rejections Under 35 U.S.C. § 102(b)

Claims 18, 19, and 27 have been cancelled rendering all § 102(b) rejections moot. These claims have been cancelled solely in an effort to expedite prosecution.

II. Rejections Under 35 U.S.C. § 103(a)

Claims 12-26 have been rejected as unpatentable over Bartlett et al. (U.S. Pat. No. 4,965,276). The Examiner alleges that the '276 patent discloses a pharmaceutical composition containing at least one compound of the formulae 1 or 2 for use in the treatment of autoimmune diseases. The Examiner contends that the compounds 1 and 2 of the '276 patent are similar in structure to those of the instant claims. The dose ranges taught are from 10 to 200 mg. The Examiner admits that the instant claims differ from Bartlett because component 2 is recited in a concentration of about 0.3% to about 50% of the first component. This is not disclosed by the '276 patent. However, the Examiner contends that it would have been obvious to the skilled artisan to combine

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the two components in this concentration range. Applicants respectfully disagree and traverse this rejection.

Applicants have discovered that "the addition of a small quantity of compound 2 to the main active component compound 1 results in a marked increase in the activity of the combination preparation." (See Specification at page 1, lines 31-33.) Table 1 at page 8 clearly shows this surprising effect. When a 5 mg/kg dose of compound 1 alone is administered to a rat, there is a 10% **increase** in paw volume and a 12% **increase** in the arthritis index. However, when administering a 4.85 mg/kg dose of compound 1 (a lower dose than the ineffective dose just described) in combination with 0.15 mg/kg dose of compound 2, there is now a 10% **decrease** in paw volume and a 5% **decrease** in the arthritis index. This effect is even more striking when 0.1 mg/kg dose of compound 2 is combined with a 9.9 mg/kg dose of compound 1 resulting in a **93% decrease** in paw volume and a **66% decrease** in the arthritis index.

Contrary to these results, the '276 patent only tests the compounds separately as seen in Tables 1, 2, and 3. As just pointed out, a dose of 5 mg/kg of compound 1 alone is ineffective. Table 1 of the '276 patent tests compound 1 **alone** at concentrations of 5, 10, 20, and 28 mg/kg. The results show that compound 1 is only significantly effective at inhibition when the dosage range reaches 28 mg/kg. Doses of 5, 10, and 20 mg/kg are ineffectual at inhibiting the deposition of immune complexes in the basement membrane of the glomeruli.

These results teach away from the dosage range taught by the presently claimed invention where compound 1 has a concentration from about 2 to about 20 mg. More

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importantly, the '276 patent does not teach that the addition of a small amount of compound 2 to compound 1 dramatically increases the effectiveness of compound 1 at these lower dosages. In addition, the dosages for compound 2 in table 2 of the '276 patent are 20 and 30 mg/kg, far exceeding the levels taught by the present invention. The highest dose claimed in the present application is 50% of compound 1. At the highest dose of compound 1 (20mg/kg), that would only be 10 mg/kg of compound 2. However, as seen in Table 1 of the present application, one need only add a small fraction of that to achieve the results disclosed.

Therefore, Applicants assert that the combination of compound 1 and compound 2 in the dosage range claimed would not have been obvious to the skilled artisan from the general teachings of the '276 patent. The '276 patent does not suggest that the addition of a small amount of compound 2 to compound 1 dramatically increases its effectiveness and activity. Nor does the '276 patent provide the necessary motivation to lower the dose of compound 1 to the ranges claimed in the present application, but rather it teaches away from lowering the concentration of compound 1.

In view of these remarks, Applicants submit that the claims would not have been obvious in view of the teachings of the '276 patent and requests that the rejection be withdrawn.

Conclusion

This application is believed to be in condition for allowance and a favorable action is earnestly solicited.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: January 28, 2000

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